Remarks

The Office Action mailed September 23, 2003 has been received and reviewed. Claim 39 having been amended, and claims 44-66 having been added, the pending claims are claims 35 and 38-66.

The specification has been amended to correct typographical errors at page 9, line 26 and page 16, line 21. Specifically, the specification originally recited "trigonal space group symmetry $P2_1$," but has now been corrected to recite "monoclinic space group symmetry $P2_1$." Applicants respectfully submit that it is obvious to one of skill in the art that $P2_1$ is a monoclinic space group symmetry as illustrated, for example, by EXHIBIT A (page 54). Claim 39 has been amended correspondingly.

The specification has also been amended at page 16, line 19, to add the recitation that "[p]referably, the crystals have one dimension of 0.15-0.8 mm, and more preferably dimensions of 0.15-0.8 mm x 0.2 mm x 0.05-0.1 mm." The amendment is supported, for example, by a recitation on page 3, lines 9-11, of U.S. Provisional Application Serial No. 60/179,261, which is incorporated by reference in its entirety at page 1, lines 10-12, of the present application. Specifically, the recitation on page 3, lines 9-11, of U.S. Provisional Application Serial No. 60/147,851 reads "[r]efinement of the condition yielded crystals of monoclinic morphology with a range of dimension of 0.15-0.8 x 0.2 x 0.05-0.1 mm" (EXHIBIT B). No new matter has been added.

Each of new claims 44, 46, 48, 50, and 52 are generally supported by the specification, and specifically supported, for example, by claim 35 and each of claims 39-43, respectively. New claims 45, 47, 49, 51, 53, and 66 are supported by the specification at, for example, page 42, lines 6-7. New claims 54 and 56 are supported by the specification at, for example, page 29, lines 22-23, and each of claims 38 and 35, respectively. New claims 55 and 57 are supported by the specification at, for example, page 15, lines 13-15. New claims 58-59 and 62-63 are supported by the specification at, for example, page 16, line 19 (as amended), and each of claims 38 and 35, respectively. New claims 60 and 64 are supported by the specification

at, for example, page 29, lines 22-23. New claims 61 and 65 are supported by the specification at, for example, page 15, lines 13-15.

Reconsideration and withdrawal of the rejections are respectfully requested.

Rejection under 35 U.S.C. §103

The Examiner rejected claim 38 under 35 U.S.C. §103(a) as being unpatentable over Kunsch et al. (U.S. Pat. Application Publication No. 2003/0054436) taken in view of Rizzi et al. (*Proteins: Structure, Function, and Genetics*, 1996; *26*:236-238) or Sambrook et al. ("Molecular Cloning: A Laboratory Manual") or Worthington ("Worthington Enzyme Manual: Enzymes and Related Biochemicals"). The Examiner also rejected claim 35 under 35 U.S.C. §103(a) as being unpatentable over Crystal Screen™ (Hampton Research) taken in view of Kunsch et al. (U.S. Pat. Application Publication No. 2003/0054436).

"To establish a *prima facie* case of obviousness . . . the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. §706.02(j). Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness, as none of the cited documents teach or suggest a crystal of *S. aureus* NAD synthetase (e.g., claim 38) or crystallizing *S. aureus* NAD synthetase (e.g, claim 35).

Specifically, the teachings of Kunsch et al. and Crystal Screen™ were discussed in the Amendment and Response submitted July 8, 2003 (pages 5-6), and are incorporated herein by reference.

Rizzi et al. disclose that "crystals of the enzyme [NAD^+ synthetase] from *Bacillus subtilis* suitable for x-ray crystallographic investigation have been grown" (Abstract). *S. aureus* NAD synthetase and *B. subtilis* NAD synthetase differ, for example, in sequence (e.g., Figure 9 of the present specification) and structure (e.g., Figures 7b, 7c, 8, and 10 of the present specification). Thus, Rizzi et al. fail to teach or suggest a crystal of *S. aureus* NAD synthetase (e.g., claim 38) or crystallizing *S. aureus* NAD synthetase (e.g, claim 35).

Sambrook et al. disclose a procedure for "production of hybrid proteins that can be cleaved with factor X_a" (Title, page 17.30). Step 7(c) reads: "Collect the cells and purify the fusion protein (see Nagai and Thøgersen 1984). Store at -20°C until needed." However, Sambrook et al. fail to teach or suggest a crystal of *S. aureus* NAD synthetase (e.g., claim 38) or crystallizing *S. aureus* NAD synthetase (e.g, claim 35).

In describing cell isolation techniques, Worthington states that "[r]econstituted enzymes should not be stored at 2-8°C. If necessary they can be aliquoted and frozen at -20°C. Avoid repeated freeze-thaw cycles" (page xiv, right column). However, Worthington fails to teach or suggest a crystal of *S. aureus* NAD synthetase (e.g., claim 38) or crystallizing *S. aureus* NAD synthetase (e.g, claim 35).

In summary, none of the cited documents, either alone or in combination, teach or suggest a crystal of *S. aureus* NAD synthetase (e.g., claim 38) or crystallizing *S. aureus* NAD synthetase (e.g, claim 35). Nevertheless, the Examiner asserted that "one of ordinary skill in the art would recognize that the utilization of recombinant techniques for the isolation/production of *Staphylococcus aureus* polypeptides (i.e. nicotinamide adenine dinucleotide) would at minimum result in a crystal (i.e., frozen for storage)" (page 3, lines 9-11 of the Office Action mailed September 23, 2003). Applicants respectfully disagree.

Applicants note that a crystal is defined as "[a] solid of regular shape and, for a given compound, characteristic angles, formed when an element or compound *solidifies slowly enough*, as a result either of freezing from the liquid form or of precipitating out of solution, to allow the individual molecules to take up regular positions with respect to one another" (EXHIBIT C, CancerWEB's On-line Medical Dictionary). In contrast, Applicants respectfully submit that the recitation "frozen for storage" suggests *rapid* cooling to one of skill in the art. Further, *rapid* cooling might result, for example, in an oily or amorphous material, but not necessarily a crystal. Applicants respectfully submit that the Examiner has mistakenly equated *frozen*, defined as "[c]ongealed with cold" (EXHIBIT D, CancerWEB's On-line Medical Dictionary), with *crystal*, which is defined herein above. Thus, Applicants respectfully submit

that the recitation of "frozen for storage" is not necessarily equivalent to the disclosure of a crystal or a method of crystallizing.

Further, Applicants respectfully submit that the relevance of the Examiner's recitation of "crystalline form (i.e., frozen, ice form, etc)" (page 3, lines 13-14 of the Office Action mailed September 23, 2003) is not clear. As discussed herein above, one of skill in the art would not equate *frozen* with *crystalline form*. Further, the meaning of "ice form" is not clear, as the term "ice" refers to "[w]ater or other fluid frozen or reduced to the solid state by cold" (EXHIBIT E, CancerWEB's On-line Medical Dictionary). Clarification of the Examiner's remarks is respectfully requested in the next Official Communication.

Applicants respectfully submit that for proteins in which crystalline forms are not known in the art, crystals of the protein, and methods of preparing the crystals, are not obvious.

> Although there is a general desire to obtain the crystal structure of any protein, the methodology of doing so is highly unpredictable and specific to each individual protein. Therefore, without guidance in the art as to how to crystallize a particular known protein, the known protein in crystalline form would be nonobvious.

Trilateral Project WM4 on *Comparative study on "protein 3-dimensional (3-D) structure related claims,"* Annex 3, Case 4, A4 (http://www.uspto.gov/web/tws/wm4/pdf/wm4_3d_annex_3.pdf). Further, the M.P.E.P. states that "[c]laims to the free-flowing crystalline form of a compound were held unobvious over references disclosing the viscous liquid form of the same compound because the prior art of record did not suggest the claimed compound in crystalline form or how to obtain such crystals." M.P.E.P. §2144.04(VII).

The Examiner has not provided any evidence that crystalline forms of *S. aureus* NAD synthetase are known in the art. Thus, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness for claims 35 and 38, and respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §103.

Allowable Subject Matter

Applicants thank the Examiner for allowing claims 39-43.

New Claims

New claims 44-53 have been added to recite methods of making the crystals of claims 39-43. Claims 39-43 have been allowed. Applicants respectfully request that claims 44-53 also be examined and passed on to allowance pursuant to M.P.E.P. §821.04. *See, for example, In re Ochiai*, 71 F.3d 1565, 37 USPQ2d 1127 (Fec. Cir. 1995) and *In re Brouwer*, 77 F.3d 422, 37 USPQ2d 1663 (Fed. Cir. 1996).

New claims 54-55 and 58-61 are directed to crystals, and each recites all the claim language of, for example, crystal claim 38. Applicants respectfully submit that new claims 54-55 and 58-61 are patentable for at least the reasons presented herein for the patentability of claim 38.

New claims 56-57 and 62-66 are directed to methods, and each recites all the claim language of, for example, method claim 35. Applicants respectfully submit that new claims 56-57 and 62-66 are patentable for at least the reasons presented herein for the patentability of claim 35.

Applicants respectfully request that the Examiner enter, consider, and pass new claims 44-66 on to allowance.

Summary

It is respectfully submitted that all the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 23 day of JANUARY, 2004, at 1:19 pm (Central Time).

By: _____
Name: SAM HER